UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,574	08/01/2002	Gerard Ribes	50319/003001	1529

21559 7590 06/27/2007

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
06/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/069,574	RIBES ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 13-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *44* is/are allowed.

6)☒ Claim(s) *1-3,5, 13-43 and 45-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/07/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The examiner for the instant application has changed. The current examiner assigned to this application is Brian-Yong S. Kwon.

2. Acknowledgement is made of applicant's filing of an amendment/remarks on 02/07/2007. By the amendment, claims 1, 15 and 16 have been amended and claims 44-46 have been newly added. Claims 1-3, 5 and 13-46 are currently pending for prosecution on the merits of the case.

3. Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

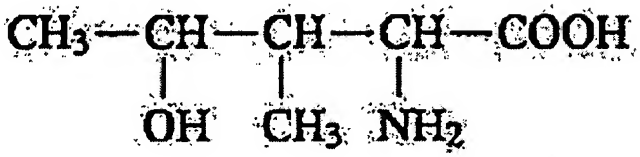
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 5, 13, 15-16, 18 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Sauvaire et al. (US Patent 5,470,879, issue date: Nov. 28, 1995).

Sauvaire et al. disclose the treatment of non-insulin dependent diabetes (type II diabetes) by the administration of 4-hydroxyisoleucine of the formula



or its lactone form or mixtures thereof (see column 7, lines 62-65), wherein the antidiabetic composition containing 4-hydroxyisoleucine is administered orally (column 2, lines 48-50). Therefore, the method of treating type II diabetes by administering 4-hydroxyisoleucine is clearly anticipated by Sauvaire et al.

With respect "the 2S, 3R, 4S isomer of 4-hydroxyisoleucine is present in the formulation" in claim 5, the interpretation of the instant claim does not limit that the 2S, 3R, 4S isomer of 4-hydroxyisoleucine is the only effective form of 4-hydroxyisoleucine being administered in the method of treatment. Since the formula as claimed is identical to Sauvaire et al.'s formula, the recitation of claim 5 is viewed as merely a characteristic of the formula where an isomer form of 4-hydroxyisoleucine is present.

Although Sauvaire is silent about the activity of said 4-hydroxyisoleucine "inducing an insulin sensitizing effect, "insulin mimetic effect", "combat insulin resistance", "reduces phosphatase activity associated with the signaling route of the insulin receptor, and/or stimulates PI3-kinase activity on IRS-1 and/or IRS-2" or "combat hyperinsulinemia", such mechanism action of said compound deems to be inherent to the prior art method. It is noted that the prior art reference directing administration of same compound or composition inherently possessing a therapeutic effects for the same ultimate purpose as disclosed by the applicant (for the treatment of type II diabetes) anticipates the claimed invention even absent explicit recitation of the mechanism of action.

The recitation of claims 2 and 3 is merely a scientific explanation for the action mechanisms of 4-hydroxyisoleucine.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Therefore, claims 1-3, 5, 13, 15-16, 18 and 23 are clearly anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 19-22, 24-43 and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sauvaire et al. (US Patent 5,470,879, issue date: Nov. 28, 1995) in view of Guittard (US Patent 5,178,867, issue date: Jan. 12, 1993).

The teaching of Sauvaire has been discussed in above 35 USC 102(b) rejection. However, Sauvaire does not specifically mention the instant administration of said compound in two or three times per day; the form of administration is a capsule or a tablet; and the use of (2S, 3R, 4S) isomer of 4-hydroxyisoleucine in the active substance 4-hydroxyisoleucine being administered for treating diabetes..

However, Sauvaire et al. disclose that the composition of 4-hydroxyisoleucine contains excipients which are chosen in accordance with the pharmaceutical dosage form adopted (column 2, lines 51-53). Sauvaire et al. also disclose that the dosage can vary within wide limits and depend on each particular case to be treated (column 2, lines 54-56). Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the dosage form of a capsule or a tablet and determine the number of administration of the drug per day for treating diabetes through routine experimentation using the teachings of Sauvaire et al. The motivation to do so is to make and use Sauvaire et al.'s invention for the treatment of diabetes and that the most convenient and economical form of drug administration is oral ingestion in dosage forms of tablets and capsules (Guittard, column 1, lines 19-24).

However, Sauvaire et al. disclose that the active substance can be of any origin, naturally or synthetically (column 2, lines 57-59). Therefore, it is reasonably interpreted that the active substance administered by Sauvaire et al. comprises all random isomers of 4-hydroxyisoleucine including the (2S, 3R, 4S) isomer as what's claimed in claims 24-43.

6. Claims 14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sauvaire et al. (US Patent 5,470,879, issue date: Nov. 28, 1995) in view of Davydov (US Patent 4,529,589, issue date: Jul. 16, 1985).

Claim 14 recite a pharmaceutical composition or a kit for the treatment of type II diabetes comprising both insulin and 4-hydroxyisoleucine.

Claim 17 recite a method of treating type II diabetes comprising administering 4-hydroxyisoleucine with the further administration of insulin.

Sauvaire et al. teach an antidiabetic composition for the treatment of type II diabetes (column 1, lines 9-10) containing as active substance 4-hydroxyisoleucine (column 2, lines 32-45). Sauvaire et al. also disclose the treatment of Non-insulin dependent diabetes (type II diabetes) by theadministration of 4-hydroxyisoleucine (column 7, lines 62-65). Sauvaire et al. do not teach insulin being administered for the treatment of diabetes. However, Davydov et al. teach that insulin is well known in the art as being used in medical practice for the treatment of diabetes mellitus (column 1, lines 14-16).

In re Kerkhoven (205 USPQ 1069, CCPA 1980) states that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose: the idea of combining them flows logically from their having been individually taught in the prior." Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine insulin and 4-hydroxyisoleucine in a pharmaceutical composition or to administer 4-hydroxyisoleucine with the further administration of insulin to a NIDDM patient, motivated by their having been taught by the prior art to be useful in treating diabetes, consonant with the reasoning of the cited case law.

Therefore, the invention as claimed in claims 14 and 17 was prima facie obvious over the combined teachings of the prior art.

Response to Arguments

7. Applicant's arguments filed 02/07/07 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that Sauvair fails to teach the instantly claimed a method of inducing insulin sensitizing or insulin mimeic effects in the tissues of patients in need thereof. Applicant alleges that stimulation of insulin secretion disclosed in Sauvaire and insulin sensitization or insulin mimetics disclosed in the instant invention are two different process, taking place in completely different cell types, thereby the teaching of Sauvaire of administering 4-hydroxyisoleucine for the treatment of type II diabetes doe not inherently anticipate the present claims.

This argument is not found persuasive. Unlike the applicant's argument, the prior art reference directing administration of same compound or composition containing same compound (e.g., 4-hydroxyisoleucine), in overlapping dosage amounts to same patient population (having non-insulin dependent diabetes) inherently possessing a therapeutic effects for the same ultimate purpose as disclosed by the applicant (for the treatment of type II diabetes) anticipates the claimed invention even absent explicit recitation of the mechanism of action. Anticipation under 35 USC 102 is an essentially irrebuttable question of fact, wherein the court stated that anticipation "cannot be overcome by evidence of unexpected results or teachings away in the art". *In re Malagari, 499 F.2d 1289, 182 USPQ; In re Spada,. 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990); In re Fracalossi, 681 F.2d 792, 215 USPQ 569 (CCPA 1982); In re Alternpohl, 500 F.2d 1151, 183 USPQ 38 (CCPA 1974); In re Wiggins, 488 F.2d 538, 179 USPQ 421 (CCPA 1973); In re Wilder, 429 F.2d 447, 166 USPQ 545 (CCPA 1970).* Indeed, a reference might reside in a nonanalogous art and yet constitute an anticipation of a claimed invention under 35 USC 102. *In re Self, 571 F.2d 134, 213 USPQ 1 (CCPA 1982).*

The prior art does not disclose the underlying pharmacological mechanism of "inducing an insulin sensitizing effect" or "insulin mimetic effect". However, the fact that the applicant may have discovered a new pharmacological mechanism for 4-hydroxyisoleucine is not considered patentably distinctive over the prior art which are directed to the same therapeutic application (for the treatment of type II diabetes).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Guittard (US Patent 5,178,867, issue date: Jan. 12, 1993) or Davydov (US Patent 4,529,589, issue date: Jul. 16, 1985) provides ample motivation to modify the teaching of Sauvaire. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Allowable Subject Matter

8. The following is an examiner's statement of reasons for allowance: The prior art reference(s) alone or in combination (USP'879-Sauvaire, USP'867-Guittard, and/or USP'589-

Davydov) in which the rejection of record is relied upon fail(s) to teach or suggest the administration of said compound which is known to have insulinotropic and antidiabetic property to patient having hyperinsulinemia.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Claim 44 is allowed.

11. Claim 1-3, 5, 13-43 and 45-46 are rejected.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
Primary Patent Examiner
AU 1614